VETOT, Volume Estimation and Tracking Over Time: Framework and Validation

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Abstract. We have implemented an effective and publicly available tool, VETOT, to track and quantify the evolution of tumors and organs over time. VETOT includes a framework both for registration and segmentation. We have evaluated the accuracy and reliability of different level set segmentation methods in order to validate this part of our software and evaluate its usability. In addition to the registration and segmentation frameworks, our program allows the creation of inter- and intra-patient atlases based on a common coordinate system defined by the landmarks selected during the registration process. Based on the National Library of Medicine's Insight toolkit, this free software is extensible and provides an intuitive interface that allows very fast processing with minimum training. This paper details VETOT and our level set segmentation evaluation.

1 Introduction

Tracking organ and tumor changes over time is a well-known problem in medical imaging [7,8]. Every organ in the human body is subject to displacement and deformations. This is particularly true in the abdominal area, which is affected by bladder and rectal filling variations. For these reasons, even within the same patient, comparing two images taken at different times can be a difficult task.

In the clinical application that motivated this research, individual uterine fibroids need to be tracked over time. This requires registering images so that the same fibroids can be recognized in consecutive images. Once corresponding fibroids are found, one wants to segment them so that, for instance, their volumes can be compared. This same need to segment features is evident in many applications where patient images are tracked over time.

We have created a tool that addresses these needs, which we call VETOT, for Volume Estimation and Tracking over Time. VETOT combines rigid landmark-based and mutual information registration and offers two different types of level

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set segmentation methods: fast marching level sets [2] and geodesic active contours [1]. We have also implemented a method for creating segmented volume atlases based on anatomical landmarks that are provided by the user during the registration process. In the rest of the paper we first provide details about the software implementation and explain how our approach has the advantage of being generic, widely applicable to the medical field and user-friendly. We then present the registration process implemented in VETOT and discuss the two level set segmentation methods that we evaluated for this application. This paper concludes with a presentation of our results and some directions for future work.

2 Description of the Software

A driving design goal for VETOT has been to minimize the requirement that users understand the mathematical details of the underlying algorithms. Some of the algorithms that we use for segmentation and registration depend on user settable parameters, but we hide almost all of these parameters from the user, either by computing them automatically, or inferring them from more intuitive user inputs.

The registration framework of VETOT only requires the user to select four anatomical landmarks in each of the two images. Typically, the landmarks are chosen to make up an anterior-posterior pair and a left-right pair, but the only requirement for registration is that they be easy for the user to find and sufficiently well-separated. The software then performs an initial rigid landmark-based registration followed by a rigid mutual information registration step that requires no further user interaction.

The segmentation process requires only slightly more human input. The user chooses a point in the interior of the region to be segmented, and another point just outside the boundary. Those two indicators are used to set a number of parameters for the segmentation algorithms. The user must also specify a number of iterations, which can be adjusted interactively if the segmented feature appears too large or too small. The geodesic active contour approach also requires a smoothness constraint that is set by choosing which one of three icons (circle, ellipse, or irregular blob) fits the overall appearance of the feature to be segmented.

VETOT makes it possible to register and segment volumes in less than five minutes. It also provides useful abilities for volume localization in three dimensions.

3 Registration

The registration framework implemented in VETOT proceeds in two stages. The process begins with a rigid landmark-based registration that roughly registers the two data sets. The registration is then refined by a rigid mutual information registration, which is known to be a consistent and accurate registration technique [6].

3.1 Rigid Landmark-Based Registration

We use landmark-based registration as a preliminary registration step because it is fast, it works regardless of the size of the initial displacement, and it provides good enough results to serve as a starting point for mutual information registration. Moreover, the landmarks provide a way to generate a coordinate system that we can use to compare data from multiple patients, and therefore to create tumor and volume atlases. The landmark-based rigid registration consists of a least square distance minimization between pairs of landmarks specified by the user.

3.2 Rigid Mutual Information Registration

We use mutual information registration [6] since it provides particularly consistent results. The intuition behind mutual information registration is that, if two images are registered properly, the value of a pixel on one image will substantially reduce one's uncertainty about the value of the corresponding pixel on the other image. The mutual information metric measures, over all of the voxels in a region of interest in the image, the total reduction in uncertainty. A gradient descent optimization is performed over the space of rigid transformations to maximize the mutual information score.

Of course, organs do not always move rigidly, especially in the abdominal cavity. However, we have found that rigid registration works well in practice. It is important to bear in mind that the principal goal of our registration is to facilitate the visual comparison of images taken at different times. Some misalignment is acceptable, but it is essential that the registration be fast. In addition, deformable registration is more difficult to analyze than rigid registration. While rigid registration produces grosser artifacts, it is easier to understand the nature of the artifacts than with deformable registration.

The landmarks specified for landmark-based registration can also serve to define the region of interest for the nutual information registration. In this way the rigid registration of a particular organ can be achieved despite surrounding deformations, and we have found that fixed parameters work in a wide range of cases.

The preliminary landmark-based registration method allows an automatic selection of a region of interest for the mutual information registration. The user does not have to perform any extra parameterization in order to register a specific organ shown in the image. Since the landmark-based registration always brings the two data sets close to one another, we are able to use fixed parameters that work generically.

3.3 Atlas Coordinate System Construction

The landmarks selected by the user during the registration process also give us the ability to create a pair of two-dimensional coordinate systems which can in turn be used to create atlases of tumor locations. To do this, we define $\mathbf{v}_1$ to be the vector from the posterior landmark to the anterior landmark, and $\mathbf{v}_2$ to be the vector from the left landmark to the right landmark. Then let $\mathbf{v}_3 = \mathbf{v}_1 \times \mathbf{v}_2$, so that that $\mathbf{v}_3$ is orthogonal to both $\mathbf{v}_1$ and $\mathbf{v}_2$. These three vectors could form the basis for a coordinate system, but they provide no natural point to serve as an origin in the physical space of the patient. Rather than arbitrarily choosing a single origin, we create two planes P and P', respectively defined by $(\mathbf{v}_1, \mathbf{v}_3)$ and $(\mathbf{v}_2, \mathbf{v}_3)$.

We define a coordinate system for P with the basis $\{\mathbf{v}_1, \|\mathbf{v}_1\|\hat{\mathbf{v}}_3\}$, where $\hat{\mathbf{v}}_3$ is taken to be the unit vector in the direction of $\mathbf{v}_3$. Thus, the two basis vectors of P are orthogonal and of the same length. Similarly, P' has the basis $\{\mathbf{v}_2, \|\mathbf{v}_2\|\hat{\mathbf{v}}_3\}$. The origin of P is placed at the right hand landmark, and the origin of P' at the posterior landmark. Using these two coordinate systems, we can identify any point p in the three-dimensional space by its projections onto P and P'. In P, the posterior landmark corresponds to $(0, 0)$, and the anterior landmark to $(1, 0)$. Similarly, in P', the right landmark corresponds to $(0, 0)$, and the left landmark to $(1, 0)$. By projecting tumor locations onto these two planes, we can get atlases of tumor locations with respect to each pair of landmarks. By suppressing the vertical component of one plane or the other, the atlases can also be merged into a three dimensional atlas in two different ways. Depending on which z-component is retained, either the anterior-posterior pair or the left-right pair of landmarks define the origin of the combined atlas.

4 Segmentation

VETOT has been implemented to use either of two level-set segmentation methods, the fast marching approach of Sethian [2] and the geodesic active countours of Caselles, Kimmel, and Sapiro [1]. As part of our development, we have evaluated and compared these two methods. In this section, we first discuss the level set methods, after which we present the results of our evaluation.

4.1 Level Set Background

Level set methods are part of the family of segmentation algorithms that rely on the propagation of an approximate initial boundary under the influence of image forces. What distinguishes them from other boundary propagation methods is that they represent the boundary implicitly as the zero level set of a function $f(\mathbf{x})$, that is, the set of points such that $f(\mathbf{x}) = 0$. It is the function f that is made to evolve based on image forces and internal smoothing forces; two benefits of this approach are that there is no dependence on parameterization, and the representation of the boundary as an implicit function allows one region to split into two, or vice versa, if the image warrants it.

It is worth noting that, whenever two algorithms are compared empirically, it is actually implementations, not merely algorithms, that are being compared. In this paper we are specifically evaluating the two algorithms as implemented in the Insight toolkit.

4.2 Fast Marching Segmentation

Conceptually, the fast marching segmentation approach generates a solution to an Eikonal equation, that is, one that characterizes the propagation of a front based only on a speed image. The speed image is based on the magnitude of the image intensity gradient, so that the speed is high where the gradient is low (i.e., away from boundaries) and the speed is low where the gradient is high. The front starts at a seed point and proceeds outward, and the output of the algorithm is a time crossing map that indicates at each pixel the time that it would take to the propagation front to reach this pixel. If the image is thresholded at a particular time, the threshold boundary indicates the location of the front at that time. The term "fast marching" actually refers to the numerical solver of the Eikonal equation. Other solvers could be used in this framework, but the fast marching method is particularly efficient.

The main advantage of this segmentation method is that it runs truly fast (less than 15 seconds on average for an image of size 384x512x131). Once the time crossing map has been computed, it is only necessary to compute the threshold in order to get a segmentation of the tumor. However, the absence of control over the shape of the front reduces the accuracy of the segmentation. In cases with low-contrast edges, this approach may be inefficient since there is no way to prevent the front from leaking where edges are not well defined. We evaluate and analyze this matter in further detail in Sec. 5.

4.3 Geodesic Active Contour Segmentation

The geodesic active contours approach is based on a more complicated differential equation that has two significant advantages. First, it is based on velocity, not speed, so that propagation can be directed inward if the front finds itself beyond the boundary of the region. Second, it responds to internal forces that tend to resist sharp curvature, reducing the tendency of the contour to leak out through small regions of low contrast. The main disadvantage of this method is that it is slower than the fast marching method. Also, the image it produces does not encode the propagation of the front over time, so one cannot quickly "rewind" to see what the front would have looked like after a smaller number of iterations.

The geodesic active contour filter needs an initial segmentation as input, rather than a simple seed point. As an initial segmentation, we use a sphere of radius equal to a tenth of an estimated radius given by the user clicks well inside and just outside the boundary of the feature to be segmented.

4.4 Preprocessing

There are a number of preprocessing steps that must be performed on an image before it can be segmentented by either of the two level set methods we use. We briefly discuss them here.

First we crop the image to a suitable region of interest, which considerably speeds up the segmentation process. The region of interest is determined based on the landmarks used to register images, and is not explicitly given by the user.

After cropping, we run a smoothing filter to reduce image noise. We use a curvature anisotropic diffusion filter [3]. Such nonlinear diffusion method is especially suitable because we wish to preserve edges, and remove point noise.

The smoothed image is then used to produce a gradient magnitude image that determines the speed of propagation of the segmentation contour. In principle the gradient magnitude image can be given to the level-sets-based method directly, but we apply a sigmoid function to emphasize the dynamic range of the boundary, and suppress it elsewhere. Such functions require that appropriate parameters be set. We determine those parameters using a histogram analysis along the line defined by user clicks.

5 Validation

The validation protocol contains three parts to estimate accuracy and reliability of level set segmentation methods implemented in VETOT.

Firstly, accuracy evaluation consists of segmenting an MR image of a surgical glove filled up with a known amount of water. We segment the same structure ten times and compare the mean to the real volume.

Secondly, reliability of the different methods is evaluated by comparing the volume of the same tumor as segmented by ten different users. We calculate the mean and standard deviation of tumor volumes. In order to estimate if increasing voxel size would allow speeding up the segmentation process without significantly affecting accuracy, we have compared the segmentation results obtained for an image with isotropic voxels to the same image with a spacing multiplied by 2 along each dimension. Each user has reported the volume estimation, the time necessary to perform the segmentation and the parameters necessary to obtain a satisfactory segmentation.

Lastly, each segmentation has been saved and then processed using Valmet, which is available at http://zeus.ia.unc.edu/public/valmet. Valmet is a tool for segmentation validation that applies a set of standard quantitative evaluation such as percentage overlap, mean/median absolute distances between surfaces and Hausdorff distance.

These results suggest that both methods are consistent even though there are some significant differences. In particular, the fast marching method actually provided more consistent performance across users. For both methods the Hausdorff distance for select users was over 10 voxels due to leakage of the contour into neighboring fibroids. Fig 3 shows an example of Haussdorf distance for both methods. The light gray values corresponds to short distance while dark gray value reflects longer distances. In Fig 3 the smoothness constraint of the

Volume (mm3)	490000
Estimated volume (mm3)	466919
Standard Deviation	13879

Fig. 1. Accuracy validation by comparison of an average segmented volume,using the geodesic active contour approach, to a known volume. The fast marching method did not give satisfactory results due to the anisotropic nature of data.

	Isotropic		*Isotropic half-size*	
	Fast Marching	Geodesic Active Contour	Fast Marching	Geodesic Active Contour
average volume(mm3)	48782	53948	47222	53931
standard deviation	6234	8267	6525	9059
average iteration	47	65	22	36
standard deviation	7	6	4	8
average time	4'30"	8'00"	3'30"	4'30"

Fig. 2. Estimation of the reliability of the segmentation method.

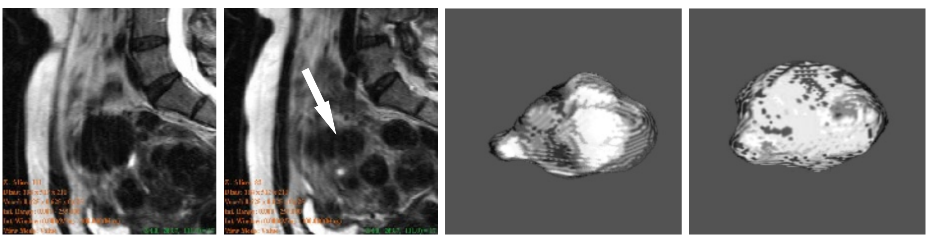

Fig. 3. This figure shows two slices of the data used for our reliability study. The two other images represent the haussdorf distance between segmented tumors obtained with the fast marching method (left) and with geodesic active contours (right). It is worth noticing that the edge at one end of the tumor is barely noticeable (pointed by the arrow). Despite the abscence of sharp edge, we can see that the geodesic segmentation results stay consistent while the fast marching technique provides abnormalities.

	Fast Marching	Geodesic Active Contour
Haussdorf distance	9.8288514	10.253
standard deviation	4.704292362	3.493

Fig. 4. This table presents the average Haussdorf distance we obtained for each segmentation method, as well as the corresponding standard deviation. We can notice that, as expected, the geodesic active contour approach provides more consistent behavior.

geodesic active contour provided additional stability to the segmentation. However, in general, geodesic active contour leakage was very sensitive to the initial seed point, the smoothness constraint and particularly the number of iterations. User reported more difficulty in adjusting these parameters to attain a desired segmentation. Fast marching leakage was dependent solely on the number of iterations. Users reported less frustration in trying to manage the parameter. We believe that these results are quite specific to the difficult nature of fibroid segmentation in these data. Nevertheless, on such clinically relevant segmentation tasks, the simplicity, speed and intuitive behavior of fast marching lead to increased clinical performance compared to geodesic active contours.

6 Conclusion

VETOT is innovative and user-friendly software that provides an efficient way to track a wide variety of volumes and tumors over time. It gives accurate and reliable results in a couple of minutes. It also allows the comparison of intra and inter-patient data for creation of atlases. This package is downloadable for free on our web site (http://www.caddlab.rad.unc.edu) and has been developed using the National Library of Medicine's Insight toolkit. It is very easy to extend and showcases the most recent medical image processing methods added to ITK. This work was supported by the NIEHS, and in part by NLM N01 LM 03501.

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